gout, urate, and crystal deposition disease

MDPI

Review

Gout and Gout-Related Comorbidities: Insight and Limitations from Population-Based Registers in Sweden

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Abstract: Population-based databases in Nordic countries offer unique opportunities for large-scale population-based epidemiological studies. The personal identity number enables researchers to link different registers at the individual level, which can be used for large-scale epidemiological population-based studies. This review outlines how these opportunities have been used so far in the field of gout research, as well as the potential challenges and limitations. Their major advantage is that they cover the entire population, minimizing problems such as selection bias and loss to follow-up. This has enabled us to provide information on gout regarding risk factors; occurrence; association with comorbidities in relation to gout onset; treatment patterns; as well as its effect on other outcomes, such as sick leave and mortality. Validity issues, missing data, and legal issues are some of the challenges that researchers need to deal with. Choosing the most appropriate combination of databases to use for a specific question is crucial in order to maximize validity and adjust for confounders. Despite challenges and potential limitations, the Swedish registers have provided valuable epidemiological results and will continue to play an important role in the years to come.

Keywords: gout; register studies; comorbidities

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1. Introduction

An association between gout and hypertension, diabetes, kidney disease, and cardiovascular disease (CVD) has been observed since the late 19th century [1]. However, at that time, there were no studies indicating that gout or urate had a causal role in these conditions. These associations were largely ignored until the mid-1950s and early 1960s when they were rediscovered [2,3]. Thereafter, many epidemiological studies on the association between gout/urate and a wide variety of comorbidities have been conducted using different methodologies and study populations.

In Nordic and some other countries, we have the option of using already existing population-based register data. Demographic, social, and healthcare data have been consistently collected for decades, providing unique research opportunities for both cross-sectional and longitudinal population-based studies (Figure 1).

The healthcare system in Nordic countries is public and tax-funded. Each resident upon birth or immigration is assigned a personal identity number, which is unique and follows the person during their whole lifespan. In register-based research, these personal identity numbers are essential because they enable the easy and accurate individual-level linkage of registries (Figure 1). This facilitates studies in large populations with rare outcomes that otherwise cannot be carried out. Individuals can be followed over long time periods, and the scientific value of these data increases continuously as we add more observation time and more people.

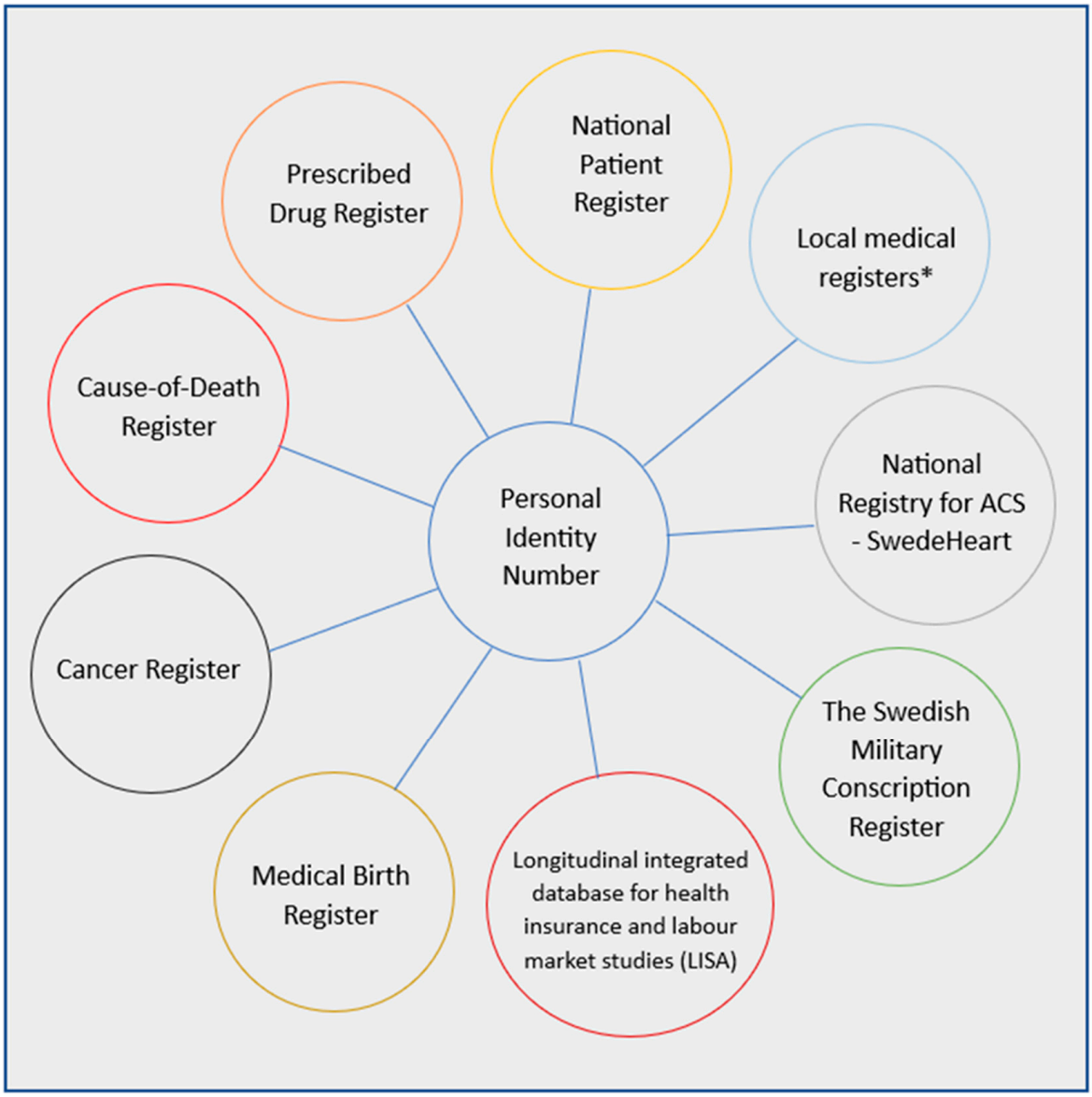

Figure 1. Linkage between Swedish databases by personal identity number. * At the regional level, covering both primary and specialized care. ACS, acute coronary syndrome.

2. Strengths

Nordic registries are population-based with virtually complete follow-up, minimizing selection bias and problems with loss to follow-up. The registries intend to include the whole population, in contrast to registries that are based on other sources: for instance, insurance databases. Data in register-based studies are prospectively collected independently of research questions, thus minimizing the risk of information bias. Furthermore, registers in Nordic countries also include valid data on social conditions, such as information regarding occupation, education level, and area of residence, that are of better quality than self-reported data [4,5]. Overall, these national registers represent a unique opportunity for conducting time-efficient and cost-effective epidemiological research (Table 1).

Nordic population-based registries are utilized for multiple research questions within various medical specialities. Within rheumatology, these registries have been used for large-scale epidemiological studies on rheumatoid arthritis, spondylarthritis, psoriatic arthritis, gout, myositis, and systemic lupus erythematosus [6–12]. Validation studies have overall supported high validity with high positive predictive values for these diagnoses [13,14].

Gout research has gained increasing attention in Nordic countries during the last decade. Population-based healthcare registers that cover both primary and specialized care, along with data linkage to other national registers, enable valid case identification and the matching of appropriate population-based controls and provide information regarding, for example, socioeconomic factors, co-morbidities, drug prescription, sick leave, and mortality. The latter can be used as both predictors and outcomes of gout and for adjustments. This approach has led to contemporary and, in some cases, novel results (Table 2). By using register data, we were able to study several gout comorbidities at the same time to address comorbidity onset in relation to gout onset. By following the patients prospectively, it was possible to study how many gout patients developed CVD over time. Gout was found to be associated with many comorbidities, and most were already present at the time of the first gout diagnosis. Women with gout had more comorbidities than men, which was related to the higher age of women at the time of gout onset [15]. Furthermore, patients with incident gout had a significantly higher risk of a first-ever acute coronary syndrome event (ACS) compared to the general population [16].

Table 1. Strengths and limitations of population-based databases in medical research.

Strengths	Challenges and Limitations
Large study population	Misclassification
Virtually complete follow-up	Missing data
Data are prospectively collected	Underestimation of some medical conditions, i.e., alcohol abuse and obesity
Data collection is independent of research questions	Difficult to study minorities and cultural differences
Time- and cost-effective	Lack of specific phenotypic data, i.e., tophi
Possibility to study multiple outcomes at the same time	Difficult to study patient's adherence and over-the-counter drugs
Possibility to study rare outcomes	
Opportunity for pharmacological studies using real-world data	
Possibility to study rare drug side effects	
Opportunity for collaborative research	

The linkage of healthcare databases to the Swedish Prescription database has enabled us to study the treatment of gout in Sweden, both the degree of initiation and persistence, trends over time, and whether treatment affects the risk of selected outcomes, such as ACS (Table 2). All Nordic countries have similarly established national databases that track prescription drugs that are dispensed to individuals at ambulatory care, aiming to assess nationwide time trends in drug utilization and carry out regional and international comparisons [17]. The registration of drugs dispensed at community and private pharmacies is mandatory, resulting in a high degree of completeness and high validity for the data [18].

Pharmacoepidemiologic studies based on registered data have some challenges (Tables 1 and 3). Primary non-adherence, defined as not filling a prescription, is not an issue as the registries have information on dispensed drugs. However, secondary non-adherence, defined as filling a prescription but not taking the drug, is more difficult to ascertain. For chronic medication, the absence of dispensing further prescriptions after a three-month interval (the longest interval for which any medication may be prescribed) can be used as a proxy for non-adherence.

Randomized controlled studies (RCTs) have the highest internal validity in clinical research. However, there are several limitations with RCTs, including generalizability due to the selection of patients (lower age, fewer comorbidities, high disease activity, etc.) and too short of a follow-up to study rare outcomes that are relevant for the evaluation of safety.

High age and many comorbidities are often the exclusion criteria in RCTs [19,20], and these are overrepresented in the gout population. Febuxostat was approved by the Federal Drug Administration (FDA) in 2009 with the comment that there were insufficient data on the urate-lowering efficacy and renal safety of febuxostat in patients with severe renal impairment, a patient group with an increased need for urate-lowering treatment (ULT) [21]. These issues can, however, be addressed in well-designed population-based register studies on large samples, real-world study populations, and long follow-up periods. Furthermore, the effectiveness of treatment can be affected by other factors that are not taken into account in strict trial protocols, such as the patient-centred approach where the physician individualizes the treatment for the specific patient by adjusting the dose or the interval, or the patient's compliance. In contrast to RCTs, where the effect of confounding factors is eliminated via randomization, adjustments for confounders represent a problem in observational register studies, which can only be partially addressed.

Registry studies drawn from large system databases represent an alternative and robust approach to demonstrate the generalizability of results from RCTs and study the safety issues of rare side effects and drug effects in real-world populations. An epidemiological approach to drug studies is therefore highly essential.

Population and register-based databases also offer an opportunity for collaborative research. The similarities between and within Nordic registries have allowed researchers to merge data from several countries, providing opportunities for research in even larger study populations with long and complete follow-ups. There are organizations that facilitate collaborative research in Nordic countries, such as NordForsk. NordForsk was established in 2005 under the Nordic Council of Ministers and facilitates and funds Nordic research [22]. This collaborative approach has resulted in unique knowledge in rheumatoid arthritis and spondylarthritis both regarding the effectiveness of different treatments (i.e., in spondylarthritis, biosimilars vs. originators of TNF inhibitors [23] IL17 inhibitors vs. TNF inhibitors [24]) as well as their effects on rare outcomes, such as multiple sclerosis [25].

The process of choosing the most appropriate database to study a specific question is both important and crucial. To study gout in Sweden, we had to restrict our analyses to regional databases to ensure the coverage of both primary and specialized care since the National Patient Register does not include primary care, where gout is primarily treated in Sweden. Regional databases have large similarities regarding the coverage of healthcare contacts; however, their starting time and the availability of laboratory data may slightly differ (Table 3). In the US, there are several large databases with individual-level data on healthcare contacts and drug use. However, most of these American claim databases were started by health insurance organizations for administrative purposes and cover only selected populations. The General Practice Research Database (GPRD) in the UK was established in 1987 and is one of the most commonly used databases in epidemiological research, containing information about healthcare contacts and drug prescriptions from primary healthcare practices, covering about 5% of the UK population [26]. The GPRD is therefore appropriate for studying diseases that are mainly treated in primary care but not those treated in specialized care.

Table 2. Register-based studies on gout using Swedish register data.

Study	Outcome of Interest	Results
Incidence and prevalence of gout in Western Sweden [10]	Prevalence, trends in the incidence of gout, and ULT use in Western Sweden in the period 2002–2012.	• The prevalence of gout was 1.8% and the incidence was 190 cases per 100,000 person years. • The incidence of gout increased significantly in the period 2005–2012 at almost 50%. • Only 42% of prevalent gout patients had dispensed a prescription of ULT in 2012.

Table 2. *Cont.*

Study	Outcome of Interest	Results
Prevalence and incidence of gout in southern Sweden from the socioeconomic perspective [27]	The prevalence and cumulative incidence of gout in southern Sweden with respect to socioeconomic status.	• The crude point prevalence of gout in 2013 was 1.69% • The cumulative incidence in 2013 was 24 cases per 10,000 person years. • Persons with middle income had the highest point prevalence and cumulative incidence of gout, while those with white collar occupations had the lowest.
Gout in immigrant groups: a cohort study in Sweden [28]	The association between country of birth and incidence of gout in different immigrant groups in Sweden.	• The risk of gout was highest among men from Iraq (HR, 1.82; 95% CI, 1.54–2.16) and Russia (HR, 1.69; 95% CI, 1.26–2.27) and high among men from Austria, Poland, Africa, and Asian countries outside the Middle East • The risk of gout was highest among women from Africa (HR, 2.23; 95% CI, 1.50–3.31), Hungary (HR, 1.98; 95% CI, 1.45–2.71), Iraq (HR, 1.76; 95% CI, 1.13–2.74), and Austria (HR, 1.70; 95% CI, 1.07–2.70) and high among women from Poland. • The risk of gout was lower among men from Greece, Spain, Nordic countries (except Finland), and Latin America and among women from Southern Europe compared to their Swedish counterparts.
Trends in Gout Hospitalization in Sweden [29]	Hospitalization trend for gout in Western Sweden in the period 2002–2012.	• The annual hospitalization rate for gout increased significantly from 9.5 to 16.7 per 100,000 adults. • The duration per hospitalization increased from 3 to 5 days. • The total inflation-adjusted annual healthcare costs for gout hospitalizations in this region increased from USD 5.21 to USD 8.15 $\times$ 10^5.
Incidence of and risk factors for nephrolithiasis in patients with gout and the general population, a cohort study [30]	The overall incidence of NL in gout cases and general population controls and risk factors for first-time NL in cases and controls separately.	• The risk (age- and sex-adjusted) of NL was increased by 60% in cases compared to controls (IRR, 1.60; 95% CI, 1.47–1.74). • Point estimates for predictive factors were similar in cases and controls, except for a significant interaction for losartan, which increased the risk of NL only in controls (HR; 1.49; 95% CI, 1.03–2.14).
Comorbidity in gout at the time of first diagnosis: sex differences that may have implications for dosing of urate lowering therapy [15]	Comorbidities at the time of first diagnosis of gout compared with matched population controls, overall, and by sex.	• All examined comorbidities were 1.2–2.5-fold more common in gout patients at diagnosis than in population controls in both sexes. • Women with gout were on average 6 years older than men at first gout diagnosis, and most comorbidities, including obesity and diuretic use, were or tended to be more frequent in women than in men. • When standardizing for age, sex differences were attenuated but women still had a higher prevalence of thromboembolism (6.6% vs. 5.2%) and COPD (3.1% vs. 2.4%) and men had a higher prevalence of CHD (9.4% vs. 6.4%), AF (9.0% vs. 6.0%), congestive heart failure (7.7% vs. 6.6%), and stroke (4.1% vs. 3.3%).

Table 2. *Cont.*

Study	Outcome of Interest	Results
Factors associated with initiation and persistence of urate-lowering therapy [31]	The proportion of gout patients in the period 2011–2013 that received and persisted with ULT after gout diagnosis, as well as predictors for start and persistence with ULT.	• 32% of gout patients received ULT within the first year after the first gout diagnosis. • Male sex, presence of diabetes or cardiovascular comorbidity, and reduced kidney function but not diagnosed as "end-stage kidney failure" increased the likelihood of receiving ULT. • 75% of those starting ULT did not persist with ULT treatment within the first 2 years. • Age < 50 years, lack of comorbidities, and "normal kidney function" or "end-stage kidney failure" were associated with non-persistence with ULT.
Work disability in gout: a population-based case-control study [32]	The extent and cost of work disability among patients with gout compared with matched population controls.	• The average work absentee rate during the 3-year follow-up period was higher among patients with gout than controls: 22% and 14%, respectively ($p < 0.0001$). • Gout was an independent predictor of new-onset absenteeism (OR 1.47; 95% CI 1.23 to 1.75).
Occupational exposure to inorganic dust and risk of gout: a population-based study [33]	The association between occupational exposure and inorganic dust and risk of gout.	• Exposure to inorganic dust was associated with gout in both unadjusted (OR, 1.12; 95% CI, 1.04–1.20) and multivariate (OR, 1.08; 95% CI, 1.00–1.16) analyses of the whole population. • In sex-stratified multivariate analyses, dust exposure was significantly associated with gout in women (adjusted OR, 1.26, 95% CI; 1.05–1.51) but not in men (adjusted OR, 1.05; 95% CI, 0.97–1.13).
Association between perinatal factors and future risk for gout-a nested case-control study [34]	Maternal and perinatal factors that are associated with the future risk of being diagnosed with gout.	• Maternal diabetes (OR, 3.1; 95% CI, 1.3–7.4), any congenital malformation (OR, 1.33; 95% CI, 1.04–1.7), and being small for gestational age (OR, 1.75; 95% CI 1.3–2.3) were associated with significantly increased risk of future gout development.
Incident Gout: Risk of Death and Cause-Specific Mortality in Western Sweden: A Prospective, Controlled Inception Cohort Study [35]	Overall and cause-specific mortality in gout.	• The risk for death in incident gout was not increased in men, but it was increased in women by 10%. • Death from CVD, renal disease, and digestive system diseases was significantly increased in the total gout population while death from dementia, cancer, and lung diseases was significantly decreased.
Incident Gout and Risk of First-Time Acute Coronary Syndrome: a Prospective, Population-Based Cohort Study in Sweden [16]	The risk of first-time ACS in a large cohort of primary and secondary care patients with incident gout compared to the general population.	• The IR of first-time ACS was significantly increased in the gout cohort compared to controls (9.1 versus 6.3 of 1000 person years). • Unadjusted Cox regression showed that gout patients had a higher risk of first-time ACS compared to controls (HR 1.44 [95% confidence interval (95% CI) 1.33–1.56]). • In multivariate analysis, the risk diminished but remained significant (HR 1.15 [95% CI 1.06–1.25]).

Table 2. *Cont.*

Study	Outcome of Interest	Results
Gout in Dalarna, Sweden- a population-based study of gout occurrence and compliance to treatment guidelines [36]	The incidence and prevalence of gout in Dalarna, as well as the use of allopurinol and compliance to treat-to-target recommendations before and after the publication of Swedish national guidelines in 2016.	• The incidence of gout was 221–247 per 100,000 person years from 2014 to 2019. • The prevalence in 2018 was 2.45%. • Among prevalent cases, the proportion of allopurinol ranged from 21% to 25%. • The proportion of patients reaching a target SU level of < 360 µmol/L was higher in the period 2016–2018 compared to the period 2013–2015 (45% vs. 30%, $p < 0.001$).

OR, odds ratio; HR, hazard ratio; CI, confidence interval; NL, nephrolithiasis; IRR, incidence rate ratio; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; AF, atrial fibrillation; ULT, urate-lowering treatment; ACS, acute coronary syndrome; SU, serum urate; CVD, cardiovascular disease.

Table 3. Characteristics of Swedish databases.

Swedish Databases	Start	Population Coverage	Limitations
National Patient Register	1964 for inpatient care and 2001 for outpatient care	≈100% coverage for inpatient care and ≈80% for outpatient care.	Primary care data not included.
Prescribed Drug Register	2005	All dispensed prescriptions at Swedish pharmacies.	Over-the-counter drugs, drugs used in hospitals, or drugs that are prescribed but not collected by the patient are not included.
Regional healthcare registers			Only partial inclusion of laboratory results. Data on smoking or BMI are lacking.
➢ VEGA	2000	Medical and administrative data for inpatient, outpatient, public and private primary care in the Västra Götaland region.	
➢ Skåne Healthcare Register	1998	Medical and administrative data for inpatient, outpatient, public, and private primary care in the region of Skåne.	
➢ Dalarna Healthcare Register	2000 for primary care and 2013 for inpatient and outpatient care	Medical and administrative data for inpatient, outpatient, public, and private primary care in the region of Dalarna.	
National Registry for ACS-SwedHeart	1995	Information about risk factors, baseline characteristics, symptoms, in-hospital examinations, treatments, interventions, complications, discharge status, and secondary prevention up to 1-year follow-up for patients admitted with ACS. Coverage >90%.	

Table 3. *Cont.*

Swedish Databases	Start	Population Coverage	Limitations
LISA	1990	Data on health insurance, parental insurance, and unemployment at the individual level for all individuals aged >16 years who are registered in Sweden on 31 December each year. Data on education level for >98% of all individuals aged 25–64 years.	
Cause-of-death Register	1961	Includes all deaths that occurred in Sweden, even deaths of persons not registered in Sweden.	
The Swedish Military Conscription Register	1969	Data on physical and psychological health of approximately 2 million individuals between 1969 and 2018, with coverage of about 90% for men born between 1951 and 1988 (conscription 1969–2006).	Exclusion of individuals with certain pre-existing medical conditions, which means that the prevalence of certain diseases is underestimated in cohorts based on this register.
Medical Birth Register	1973	All pregnancies leading to childbirth in Sweden since 1973.	Missing data, i.e., smoking during pregnancy.
Cancer Register	1958	Data on cancer cases in Sweden.	

ACS, acute coronary syndrome; LISA, longitudinal integrated database for health insurance and labour market studies; BMI, body mass index.

3. Limitations

Historically, in Sweden, the medical community has expressed doubt regarding the validity of gout diagnosis due to the risk of misclassification (Table 1). However, a validation study showed that the ICD-coded diagnosis of gout in both primary and specialized care in western Sweden had a positive predictive value of $\geq$80%, although monosodium urate crystal identification was rarely used to establish the diagnosis [14].

The validity of ICD-coded diagnoses also depends on the assessment tools, which may have improved or become more available over time, as in the case of heart failure [37]. Here, we see an increase in the incidence of heart failure, which partly depends on the discovery of a new entity: heart failure with preserved ejection fraction, HF–PEFFF [38]. Furthermore, the definition of hypertension has developed from a diastolic blood pressure of >115 mm Hg in the first study to show the benefits of anti-hypertensive treatment [39] to a broader definition of >130/80 mm Hg, which includes almost half of the adult US population [40].

As mentioned before, there are separate registers for diagnoses made in primary and specialized care. The National Patient Register (NPR) collects all inpatient care in Sweden since 1964 and, from 2001, all secondary outpatient care from both private and public caregivers but not data from primary care (Table 3). In Sweden, as in many other countries, most gout patients are diagnosed and solely managed in primary care. Gout research performed on individuals retrieved from the NPR (diagnosed with gout in secondary care) may not be representative of the total gout population, which is reflected in a previous Swedish study examining the prevalence of gout in immigrant groups [28]. The authors found an increased risk of gout in men born in Iraq and Russia and in women born in Africa, Hungary, Iraq, and Austria.

Missing data are a problem in some register studies. The Swedish Medical Birth Register collects information on all pregnancies that have resulted in childbirth in Sweden since 1973 [41]. Data on previous pregnancies, smoking, gestational length, method of delivery, morbidity in mother and child, and characteristics of the newborn are collected. However, data on smoking during pregnancy were missing in 50% of the registry's first 15 years, which hampered the findings of this study regarding perinatal factors and the future risk for gout [34]. Maternal diabetes and being small for gestational age increased the risk for future gout but adjustments for maternal smoking could not be performed due to missing data. Furthermore, laboratory data, such as urate levels, are only partially included in Swedish databases, affecting their use in register-based studies.

Only individuals who actively seek treatment are captured by hospital or medical prescription records. In other words, those who are not diagnosed are not included in the exposure groups, implying that the actual at-risk population is underestimated. This issue varies with diagnoses, being more pronounced for diagnoses such as alcohol abuse, depression, obesity, and smoking and less for diagnoses which almost always lead to healthcare utilization, such as ACS or cancer. We performed a register study on comorbidities at first gout diagnosis compared to non-gout controls. The diagnoses of alcohol abuse and obesity were found in 4.0% and 10.4% of gout patients, respectively, compared to 2.2% and 3.9% in non-gout controls, respectively [15]. Nationwide questionnaire studies from the Swedish National Board of Health and Welfare estimate the Swedish prevalence of alcohol abuse to be at 4% and obesity (BMI $\geq$ 30 kg/m^2) at 16% [42]. Lundin et al. in their study on the prevalence of alcohol abuse in Sweden proposed one way of dealing with this problem in register studies. By combining data from five different registers, the frequency of alcohol abuse increased by 60% [43].

The Swedish Military Conscription Register (SMCR) was started in 1969 (Table 3). In Sweden, conscription around the age of 18 years was mandatory for young men until 2010. For the 1951–1987 birth cohorts, the register has a population coverage of approximately 90% for men. Data on physical and cognitive ability were collected together with electrocardiograms, the erythrocyte sedimentation rate (ESR), and proteinuria [44]. These exposure data from young adulthood have been used for longitudinal studies of outcomes later in life. Some examples of this are a case–control study by Lundin et al. that found that 1.8% of conscripts with future end-stage renal disease had an ESR of $\geq$ 15 mm/h at conscription compared to 0.4% in controls [45], and the study by Fardell et al. that demonstrated a high ESR was inversely related to later Parkinson's disease [46]. However, severe disease could qualify for exemption from military service. Thus, the prevalence of such diseases is underestimated in the SMCR population [44].

It is often claimed that having exact dates available in the registers is an advantage. However, those dates are typically the date of diagnosis and not the onset of disorders. One may consider the acute and severe symptoms of a gout flare as something that would render a definite diagnosis at the first event, but Liddle et al. showed, in their study from 2015 on patients' experiences from initial symptoms to gout diagnosis, that this was not the case [47]. Besides patient factors, female sex and attacks in the joints other than the first metatarsophalangeal joint delayed the diagnosis. Furthermore, administrative definitions for gout flares, for instance, practitioner visits followed by prescriptions of corticosteroids, colchicine, or NSAIDs, have not been used or tested in Swedish databases.

An important ongoing question in gout research is the causality between gout and its comorbidities. Would the better treatment of gout result in an altered risk for ACS, chronic kidney disease, or neurodegenerative diseases? The insidious onset of Alzheimer's and Parkinson's diseases aggravates the attempts to relate gout diagnosis, levels of urate, and urate-lowering treatment as possible risk factors [48]. On the other hand, the Swedish national register for ACS, Swedeheart, collects data from all hospitals in Sweden that manage patients with ACS (Table 3). Patients with symptoms suggestive of ACS are enrolled at the time of admission to the hospital and are followed for 12–14 months regarding secondary prevention. In the Swedheart study by Mohammad et al., they report

an increase in the frequency of ACS during Christmas and the Swedish Midsummer celebration but no increase during the Olympic games. The most common time of day for ACS symptom onset is 10 AM, but on Christmas Eve, this is not the case as the symptoms start at 10 PM (in Sweden, Christmas Eve on 24 December is the main day of Christmas festivities) [49].

The impact of ethnicity on gout is well known and partly reflected in the large variations of gout prevalence worldwide. Cultural backgrounds are difficult to assess in registers, especially in Sweden where it is controversial to register ethnicity. In addition, it is prohibited to register information on religion, political views, and trade union membership. Data on the country of birth are registered at a limited degree [50]. One way of partly overcoming this could be name-based ethnicity classification [51].

Finally, Swedish databases have limited availability to non-Swedish investigators, and they are not amenable to queries via natural language processing technologies.

4. Will Register-Based Research Change in the Future?

The development and broad introduction of new medical record databases will probably lead to greater possibilities to extract more data into registers, especially phenotypic data such as BMI, smoking, and tophi. It would also help to find participants fulfilling the criteria for participation in RCTs [46]. However, it is important to keep these research questions in mind when designing new systems for clinical records to facilitate future data retrieval and allow for data extraction on a national level.

The General Data Protection Regulation (GDPR) was decided upon by the European Union (EU) in 2016, and it regulates the processing of personal data and the free movement of such data in the EU. It has brought many challenges to the research community, maybe because the GDPR was intended as a law of general applicability that would offer protection to personal data when processed in all sectors of the EU economy, the unique challenges it has created for the research enterprise were likely unanticipated and unintended [52]. There are many issues regarding GDPR and research, and some of the most noticeable are the new understanding of anonymized and pseudonymized data, challenges regarding consent to research, and the cross-border transfer of personal data [52].

Artificial intelligence (AI) is on everyone's lips these days and will definitely add new dimensions to register research: for instance, allowing for a much more specified retrieval and analysis of big volumes of data [53]. However, the other side of this coin contains big unanswered questions regarding the originality of work, validity of data, and whether a chatbot can be a co-author in a scientific publication [54].

5. Conclusions

The existence of population-based medical databases is crucial for epidemiologic research. Epidemiological studies following the whole population for decades are important in medical research. Registries provide great research possibilities, but to make the best use of this resource, researchers and readers need to be aware of their limitations and know what kind of questions can be addressed in these databases and why the same question may result in different answers in different databases.

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